Citation:

Wu K, Giovannucci E, Byrne C, Platz EA, Fuchs C, Willett WC, Sinha R. Meat mutagens and risk of distal colon adenoma in a cohort of US men. *Cancer Epidemiol Biomarkers Prev.* 2006 Jun; 15 (6): 1,120-1,125.

PubMed ID: 16775169

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To prospectively examine the associations between heterocyclic amine and meat-derived mutagenicity and risk of developing colon cancer.

Inclusion Criteria:

- Participant of the Health Professionals Follow-up Study, which began in 1986 and is made of of male health professionals
- Had a large bowel endoscopy between 1996 and 2002.

Exclusion Criteria:

- History of ulcerative colitis or cancer (except for non-melanoma skin cancer and organ-confined prostate cancer) or colorectal polyps before 1996
- Those who did not respond to the 1996 questionnaires, those who left the entire cooking method section blank, did report doneness but not frequency of meat intake of at least one cooked meat item, or did not have information on bacon intake from the 1994 food-frequency questionnaire (FFQ).

Description of Study Protocol:

Recruitment

Participants of the Health Professionals Follow-up Study were male health professionals who returned a baseline questionnaire in 1986 on medical history and lifestyle factors.

Design

Prospective cohort study.

Dietary Intake/Dietary Assessment Methodology

- Nutrient intake was computed by multiplying the nutrient content of foods with the reported frequency of intake of each of the foods from the 1986, 1990, 1994 and 1998 food FFQs
- Cumulative updated nutrient intake was computed by averaging the nutrient intakes from all available questionnaires before the beginning of each two-year follow-up period
- The cooking method questions were administered in the 1996 questionnaire.

Blinding Used

Not applicable.

Intervention

Not applicable.

Statistical Analysis

- Multivariable logistic regression was used to calculate odds ratios (OR) to assess associations between dietary variables and adenoma risk
- Trends were assessed by adding a continuous variable using the median for each quintile of the exposure to the multivariable models.

Data Collection Summary:

Timing of Measurements

- FFQs were administered in 1986, 1990, 1994 and 1998
- Cooking methods were assessed in 1996
- Colon adenoma cases were identified between 1996 and 2002.

Dependent Variables

Distal colon adenoma: For men who reported a diagnosis of a colorectal polyp on their biennial follow-up questionnaire, medical records were reviewed and cases were confirmed by pathology reports.

Independent Variables

- FFQs were used to assess meat intake and cooking methods and the Charred Database was used to determine the amount of heterocyclic amines and meat-derived mutagenicity in meats.
    - Meat intake (servings per day)
    - Meat-derived mutagenicity intake (revertant colonies per day)
    - 2-amino-3,8-dimethylimidazo[4,5,-f]quinoxaline (MeIQx) intake (ng per day)
    - 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) intake (ng per day)
    - 2-amino-3,4,8-trimethylimidazo[4,5,-f]quinoxaline (DiMeIQx) intake (ng per day).

Control Variables

- Age
- Family history of colorectal cancer

- Reason for endoscopy
- Negative endoscopy before 1996
- Physical activity
- Smoking status
- Race
- Aspirin use
- Total energy intake
- Calcium and folate intake.

Description of Actual Data Sample:

- *Initial N:* 51,129 (original cohort)
- *Attrition (final N):* 14,032 (after applying exclusion criteria)
- *Age:* Not reported
- *Ethnicity:* Primarily White
- *Other relevant demographics:* Health professionals
- *Anthropometrics:* None
- *Location:* United States.

Summary of Results:

Key Findings

- Between 1996 and 2002, 581 distal colon adenoma cases were identified
- Total red meat, hamburger, beef/lamb/pork as main dish and chicken/turkey were not associated with distal colon adenoma before or after adjusting for MDM or MeIQx (meat mutagens)
- There was a positive association between higher intake of processed meat and risk of adenoma (multivariate OR of extreme quintiles=1.52; 95% CI: 1.12, 2.08; P=0.02). This association was 1.46 (95% CI: 1.06, 1.99; P for trend=0.04) and 1.47 (95% CI: 1.06, 2.04; P for trend=0.05) after adjusting for MDM and MeIQx, respectively
- Higher intake of meat-derived mutagens was marginally associated with increased risk of adenoma [fourth vs. lowest quintile: Odds ratio (OR), 1.39; 95% confidence interval (95% CI), 1.05-1.84; highest vs lowest quintile: OR, 1.29; 95% CI, 0.97-1.72; P=0.08) and adjusting for total red meat or processed meat intake only slightly attenuated these associations.

Other Findings

- There was a suggestion of a positive association between 2-amino-3,8-dimethylimidazo[4,5,-f]quinoxaline (MeIQx) and risk of adenoma, but this association was attenuated after adjusting for processed meat intake
- 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and 2-amino-3,4,8-trimethylimidazo[4,5,-f]quinoxaline (DiMeIQx) did not seem to be associated with the risk of adenoma
- Chicken and turkey intake was not associated with adenoma risk.

Author Conclusion:

Higher intake of meat-derived mutagenicity was marginally associated with increased risk of adenoma, and adjustment for total red meat or processed meat intake did not explain these associations.

Reviewer Comments:

Study Strengths

- *The use of several FFQs enhanced the estimate of long-term dietary intake*
- *Detailed FFQs allowed for adjustment for several possible confounders.*

Study Limitations

- *Heterocyclic amine and meat-derived mutagenicity intake were based on a limited number of cooking method questions*
- *Misclassification of exposure may have occurred due to certain factors such as the frequency of flipping of the meat during the cooking process or the thickness of the meat*
- *Cooking methods were only assessed once*
- *The interactions between heterocyclic amine intake and genetic polymorphisms or metabolic enzymes were not assessed.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes

2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	N/A
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes

5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	???
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes

7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes